

Aus der Universitäts-Kinderklinik Bern (Jenner-Spital)

Direktor: Prof. Dr. E. Glanzmann

DIABETES MELLITUS IN CHILDREN

INAUGURAL-DISSERTATION

zur

Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität Bern

vorgelegt von

Ezra Dorison

von New York, USA

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INTRODUCTION

Diabetes Mellitus must be thoroughly understood before one can attempt to go into the special problems pertaining to the child. A few general remarks will, however, be made in this paper.

Diabetes Mellitus is a disease of metabolism. It is not the purpose of this paper to deal in detail with the complex physiological disturbances. Perhaps an adequate picture of the disease can be obtained from the following three diagrams, in which the width of the arrows are a quantitative indication of the reactions.

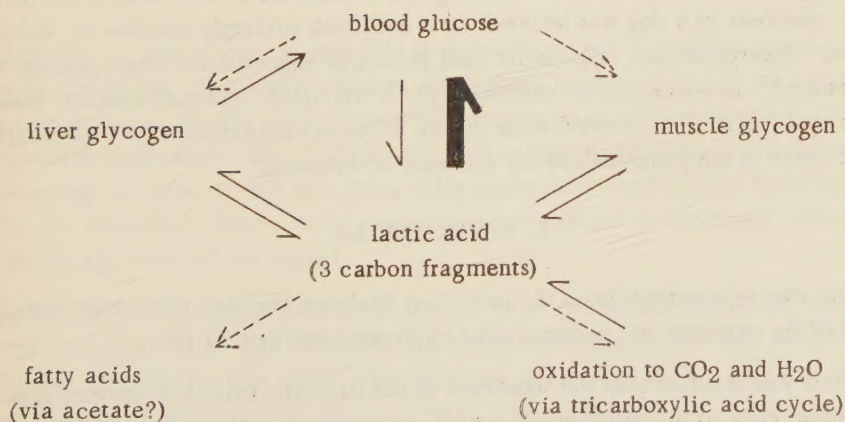
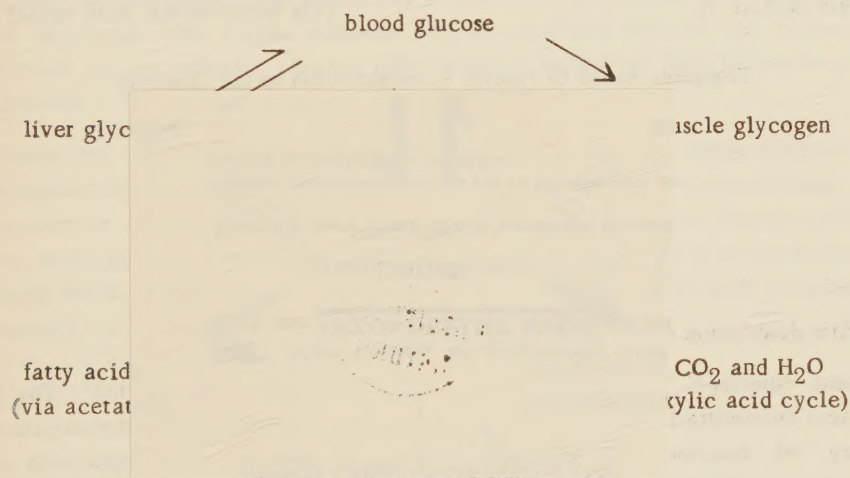
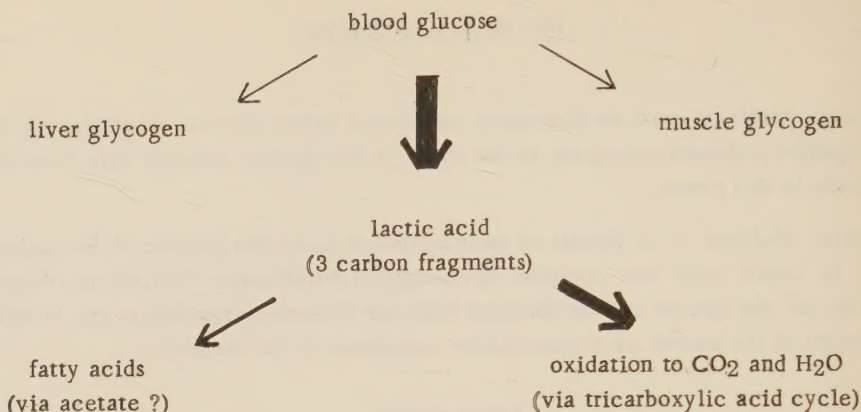


Diagram of Carbohydrate Metabolism in Diabetes Mellitus



Processes Aided by Insulin Administration to the Diabetic

HISTORY

A. UNTIL INSULIN

The first description of the disease was clinical.

Aretaeus described "a melting down of the flesh and limbs to urine". The first chemical demonstration of the disease was made by Thomas Willis in the seventeenth century. He described the sweetness of the urine. Dobson, in the eighteenth century, demonstrated the presence of sugar in the urine. A significant step was the physiological demonstration by Von Mering and Minkowski in 1889, that the removal of the pancreas of a dog was followed by a condition strikingly similar to diabetes in man. Hyperglycemia, glucosuria and ketonuria appeared and when glucose was administered, it was excreted quantitatively in the urine. Histopathological studies in man by Opie in 1900, showed some degree of correlation between the degeneration of islet tissue in the pancreas and the presence of diabetes.

B. AFTER INSULIN

The final step which established the proof that Diabetes Mellitus arises from intrinsic disease of the pancreas was accomplished by Banting and Best in 1921.

It is from this point on that the treatment of the diabetic child has assumed special importance. Prior to the discovery of insulin, treatment was identical to that of adult diabetes, namely diet restriction which, nevertheless, was followed by the inevitable diabetic coma.

In recent years further study by men such as Houssay, has indicated that not only the pancreas, but also such glands as the pituitary, thyroid and adrenals play a vital role in the evolving of Diabetes Mellitus. These works, however, seem not to apply too greatly to the child diabetic. Here, without question, the main problem is one of hypofunction of the islet cells of the pancreas.

OBJECT

Why and when some children are afflicted is one of the problems that will be considered in this paper. The course and treatment of the disease in the child will also be discussed. The various problems will be considered with the aid of other papers written on this subject, plus the information to be derived from textbooks and case histories at the "Jenner Kinderspital in Bern".

There are what might be termed the classical conceptions. Some of these will be supported in this paper while some may be disputed. They are, nevertheless, a firm foundation upon which all future developments in regard to the diabetic child must be built; that some have been recently changed and modified is not to detract from their worth as the basis from which all future developments must of necessity be derived.

ETIOLOGY

A. HEREDITY

Heredity is said to play a vital role in determining which children will be afflicted with the disease. That every child in whom there is a tendency will develop diabetes is not the case, but this vital factor when combined with such infections as diphtheria, parotitis epidemica, etc., may very well lead to the emergence of diabetes. Interesting to note is that in a great many cases where heredity has been assumed to be an important factor, each succeeding generation has developed diabetes at an earlier age than did the parent.

Some interesting studies have been carried out in the United States. An unusual one was recently made, the subjects all being under one year of age. The following figures summarize this study. They span the years from 1850 - 1947 and are based on reports of physicians all over the world. Twenty-eight cases were compiled, of which seventeen had a negative family history. It must, however, always be kept in mind that a negative history does not exclude the possibility because it may be

unknown. Of the eleven with a positive family history, the relationships were as follows:

1. Father's aunt
2. Grandfather
3. Grandmother
4. Mother
5. Paternal grandmother
6. Mother
7. Maternal grandmother, maternal aunt
8. Mother
9. Paternal uncle
10. Paternal grandmother
11. Maternal aunt, maternal cousin

The transmission from the paternal or maternal side is evident. In a survey taken at a diabetic summer camp in the United States, it was found that among boys ranging in age from 5 - 16.9 years, heredity was positive in 62 %.

Another study concerning twins was made. Nineteen pairs of similiar twins and twenty-five pairs of dissimilar twins with diabetes in the family were studied. Of these, 62 % of the similiar group and only 7 % of the dissimilar group developed the condition.

There is an agreement among many authorities that the tendency for diabetes is transmitted as a recessive factor and that the following are possibilities:

1. All offspring will have diabetes if diabetic persons intermarry.
2. One-half the offspring will be diabetic if a diabetic person marries a non-diabetic with a family history.
3. One-fourth the offspring will be diabetic if two non-diabetic persons with family histories marry.
4. None of the children will be diabetic if a diabetic person marries a normal person with no hereditary background of the disease.

B. INFECTION

The role of infection is now being stressed as one of the important factors in the etiology of diabetes. There have been numerous studies with a figure of 35 % to 40 % most often quoted. That it precipitates diabetes and increases the severity in cases already developed has been shown. A sharp rise in the incidence of diabetes was noted after an epidemic of influenza in the United States. That infections cause an increase in blood sugar curves was shown by Goetzky in 1920. John, in 1934,

reported that 33 cases of the disease had occurred within thirty-eight days after an infection and he based the hyperglycemia in five possibilities:

1. Reduced insulin output
2. Inability of liver and muscles to store glycogen readily
3. Interference with action of insulin
4. Non-function of the nervous control mechanism
5. Increased epinephrine output.

Another report by Ladabure in 1938, showed that acute infectious diseases had preceeded diabetes by 90 days in 23 % of the cases. The question, of course, arises as to the family histories of these children.

C NERVOUS DISORDERS

In what appears to be more than a coincidence, diabetes has seemed to be associated with central nervous system disorders (12,5 % in one series). These disorders take the form of head injuries, hydrocephalus and microcephalus. The link between the central nervous system disorders and the diabetic symptoms seems to be a derangement of carbohydrate metabolism. Obesity, hyperthyroidism and overnutrition seem to play no role in the etiology among children.

SYMPTOMS

The beginning of diabetes in a child is, unlike that of the adult, a sudden and violent occurrence. Thirst, polyuria, weakness, increased appetite and loss of weight develop quickly.

In as much as the needs of the child are greater for carbohydrates than are those of the adults, it tries to compensate when the normal carbohydrate metabolism is interfered with, by attempting to convert fat and protein. This leads to acidosis which is the real danger in the child. Glucosuria is, in itself, not to be feared, in fact, a trace of sugar is the ideal regulatory point. The diabetic coma is characterized by dry skin and quick pulse.

There are certain features which, though not diagnostic, should make one suspect diabetes in the child. In a recent study made in the city of New York on forty-eight children the following figures were noted:

1. Loss of weight	54 %
2. Cutaneous involvement	54 %
3. Polydipsia	39,6 %

4. Polyuria	25 %
5. Gastrointestinal disorder	22,9 %
6. Infection of respiratory tract	20,8 %
7. Irritability	16,7 %
8. Acidosis	16,7 %
9. Polyphagia	14,6 %
10. Disorder of central nervous system	14,6 %
11. Coma	12,5 %

These signs, together with a family history, should lead one to suspect diabetes.

In doing any work in connection with the diabetic child, one must be aware of what may be termed "pseudo diabetes". There is probably no case of cured diabetes which has been confirmed; however, what may occur is a transitory condition with hyperglycemia, ketonuria, glucosuria, which give the impression of diabetes. In these cases it has been suggested that there was an encephalitic or toxic influencing of the carbohydrate regulating brain center. The infection itself is not capable of producing genuine diabetes. However, the infection may occasionally aggravate a developing diabetes or bring a latent case to light. In "pseudo diabetes" insulin treatment may have some value.

PHYSICAL FINDINGS

A. HEIGHT AND WEIGHT

Much has been said concerning the height and weight of the diabetic child. In a study of 123 boys under insulin and dietary regulation in the United States, the following figures were arrived at:

Age	Number of Children *	Normal Weight in Kilograms	Average Weight of Diabetic Child
5	4	16 - 19,6	22,3
6	6	17,7 - 22,1	23,6
7	6	19,5 - 24,2	28,5
8	10	21,5 - 26,5	28,5
9	9	23,5 - 29,3	30
10	13	25,9 - 32,5	34,5
11	18	28,6 - 36,1	36,9
12	14	31,5 - 39,6	40,9
13	18	34,5 - 43,5	45
14	11	36,9 - 46,8	50
15	10	40,6 - 51,5	50,9
16	4	43,6 - 55,5	58,6

* The figures quoted as normal here are taken from Engelbach, W. Endocrine Medicine.

In a height survey made with the same group the following was shown:

Age	Number of Children	Normal Height in Centimeters	Average Height of Diabetic Child
5	4	103 - 110,5	111,75
6	6	108,75 - 116,24	114,75
7	6	114 - 122	125,75
8	10	118,75 - 127,25	131
9	9	123,75 - 132,25	134
10	13	128,5 - 137,5	138,75
11	18	133,25 - 142,75	142
12	14	138 - 147,5	147
13	18	142,25 - 152,25	152,25
14	11	146,5 - 157,5	158,25
15	10	150,75 - 161,25	161,75
16	4	154,5 - 165,5	167,5

It is obvious from the above two tables that the diabetic children are heavier and taller than normal children in a similar age group. Andrup, however, reports that of fifty-one children, aged two to twelve years, treated from 1935 - 1949, there were thirteen (eight boys and five girls) who were classified as dwarfs. The dwarfism was of pituitary type except in one girl who displayed hyperthyroidism. This report which points out a condition in approximately 25 % of the children is not supported anywhere else in the literature and it is difficult to comprehend how such a high percentage could escape unnoticed in the rest of the medical world. That the report is inaccurate or that the patients were atypical must certainly be the case.

B. LIVER AND SPLEEN

In the same group there were two instances of enlargement of the liver but in no cases could the spleen be felt.

C. EYES

Eighty-nine children received a fundusoscopic examination and of these, eighty-three was regarded as normal. Of the six abnormalities, two showed lense opacities, one had congenital cataracts, one had exudatelike spots in the macular region, and two showed aneurysmal dilations of veins.

D. VESSELS

Tests for capillary fragility were entirely negative.

LABORATORY STUDIES

In the same group of boys the following was brought out:

A. ALBUMINE

One child had a one plus albumine, while four others showed a trace.

B. HEMOGLOBIN

The range of hemoglobin in 109 children was 14,3 - 15,0 with an average of 12,7 gms. per 100 c.c.

C. BLOOD CHOLESTEROL

The blood cholesterol ranged from 125 - 258 mg. with an average of 173 mg. per 100 c.c.

Rabinowitch, in "The Cholesterol Content of Blood Plasma" in 1929, observed a positive correlation between total cholesterol and required insulin dosage in juvenile diabetes.

D. PROTEIN

Protein values ranged from 6,05 - 7,40 per 100 c.c. with an average of 6,49 gms.

E. SERUM ALBUMINE

Serum albumine varied from 4,11 - 5,03 gms. with an average of 4,56 gms per 100 c.c..

F. SERUM GLUBULIN

Serum glubulin ranged from 1,18 - 2,43 gms. with an average of 1,93.

G. BLOOD VESSEL CALCIFICATION

No evidence of calcification in any arteries was observed by roentenogram.

H. TOTAL AND FRACTIONAL LIPID LEVELS

In a study made on total and fractional lipid levels in diseases of childhood made by Thomas in 1947, in Chicago, the following concerning the diabetic child was revealed: (the conclusions are based on eight cases)

1. A majority of the eight had high normal to slightly elevated total lipids.
2. In most cases this was accounted for by rises in both the phospholipid and the total cholesterol.
3. Cholesterol partition was normal in all but one patient whose ester cholesterol was reduced (ratio of ester cholesterol to total cholesterol, .33).

In none of the eight diabetic children was the diabetes seriously out of control at the time of the study, though glucosuria was present. The lipid elevations that occurred in this group did not necessarily accompany either high blood sugar levels or treatment with large doses of insulin.

I. SERUM POTASSIUM, MAGNESIUM, AND CALCIUM LEVELS

In a study made by Eastman and Martin, titled "Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis", the following was the data:

1. Extreme acidosis and hemoconcentration on entrance.
2. Fall in serum potassium concentration during therapy reaching values as low as 1,9 - 2,8 milliequivalents per liter in some patients.
3. Slightly low to normal sodium levels on entry with relative constancy of sodium levels during therapy despite administration of large amounts of sodium intravenously.
4. Normal or slightly elevated magnesium levels on entry with a striking fall in concentration during the first twenty-four hours of therapy.
5. A fall in the majority of calcium concentrations to normal range and the occurrence of slight drops in concentration with therapy.
6. Variations with blood sugar levels on entry from 285 - 1092 milligrams per 100 c.c. and carbon dioxide combining powers to below 9 milliequivalents per liter.
7. Variation in doses of insulin given from 110 - 1000 units during the first twenty-four hours.
8. Parenteral administration of fluid in the first twenty-four hours ranging from 4 - 12 liters, sodium chloride from 10,5 - 27,5 gms. and dextrose from 39 - 350 gms.
9. Variations in clinical state from coma to consciousness.

The results of this study were that the fall in potassium concentrations may be related to the effect of insulin on nitrogen storage or urinary excretion and in passage of glucose, phosphorous, and potassium into muscle cells or into the liver in glycogen formation. There was a lack of constant correlation between calcium concentrations and iodized calcium levels. There was some indication of a correlation between the degree of coma and the elevated magnesium levels.

J. PROTEIN-BOUND IODINE LEVELS

In a study of protein-bound iodine levels in normal and in diabetic children made by Danowsky, Huff, Erhard, Price, Brown, Worth, Stevenson, in Pittsburgh in 1952, the following was concluded. Based on sixty-four apparently normal children aged 6 - 18 years the serum protein-bound iodine levels averaged $7.7 \pm .8$ gamma per 100 milliliter. In a comparable number of children under treatment for diabetes mellitus the average value for protein-bound iodide was found to be statistically indistinguishable. A trend towards lower levels was evident in the early adolescent years in diabetic as well as non-diabetic children.

Since serum concentration of protein-bound iodide is a reliable measure of thyroid function it may, therefore, be assumed that thyroid function plays no role in juvenile diabetes.

K. GLYCOGENESIS

Glycogenesis in the course of diabetes is extremely rare. Instances of hepatic steatosis are likewise rare. Hansen of Copenhagen reported thirteen cases, all under twenty years of age.

TREATMENT

Regulation is a combination of diet and insulin treatment. But amounts which have proven satisfactory at one point in a child's life may be totally incorrect a short while later because of spontaneous reactivation of some of the islet cells and changes in the metabolism due to the most routine of childhood infectious diseases.

An accepted basis from which regulation can be attempted is ten gms. of carbohydrate, 2 gms. of fat and 2 gms. of protein per kg. of body weight.

The proper use of insulin is a delicate skill and misuse can lead to hypoglycemia with serious consequences for the child. Correctly, insulin can be used to enable administering of adequate carbohydrates to insure the proper growth of the child. Insulin shock comes not only from a low blood sugar but also from too sudden a drop. The point at which symptoms develop may be well above the value where glucosuria occurs. The symptoms of shock are varied. Some children react violently while others become drowsy and weak.

There have been improvements upon regular insulin which allows a decrease in the number of injections that the child must undergo daily. Globin insulin and protamine zinc insulin are two of these. The principle upon which this is based is that the time

that the insulin takes affect is staggered so that the patient has a supply upon which to draw over a longer period of time. In the regulation of the diabetic child, diet combined with various mixtures of types and amounts of insulin are employed

As a matter of interest a report by Winter, Vargus and Lewin, in 1951, described implantation of protamine zinc insulin in eight diabetic patients, six children and two adolescents. The purpose was to attain better control of the disease than through routine insulin injections. The implants were of either pure protamine zinc insulin or of this drug with added cholesterol. They were placed in the subcutaneous tissues of the infrascapular or gluteal regions. In three cases a partial replacement of the daily insulin dose was attained while in the remaining five patients a total replacement of twenty to eighty-one days duration was seen. The purpose of the cholesterol in this experiment was to insure more regular absorption.

L. Nassi in 1943, reported that pantothenic acid increases and prolongs the hypoglycemic action of insulin.

A. TREATMENT IN COMA

The most serious situation which requires immediate treatment is that of the diabetic coma. Vital, are intensive insulin therapy and a sufficient rehydration of the child by isotonic sodium chloride solution in the first six hours. An opposing view, held in such places as the clinic of Professor Brdik in Prague, is that glucose should be administered at the beginning of treatment. In a comparison made in Copenhagen, twenty patients in similarly severe coma were treated. Ten were treated with glucose and insufficient insulin during the first hours while ten others were treated with intensive insulin therapy and rehydration. Three of the children treated by the former method died, whereas, all that were treated by the second method survived. The duration of coma was also shortened by 50 %.

B. FREE AND REGULATED DIET

In the every day management of the diabetic child there are two schools of thought. One favors the method of sufficient food to insure growth plus enough insulin to prevent a strong glucosuria, while the other believes in the so-called free diet with adequate insulin. At "The Jenner Kinderspital" in Bern, the former method is employed.

In the management of 123 diabetic boys in a summer camp in the United States, the long tested method of insulin plus diet regulation was employed. A summary of the diets used is seen in the following table in which the figures quoted are averages: (the figures refer to a twenty-four hour period and the weights are in gms.)

Age	Carbohydrates	Protein	Fat	Calories
5 - 7.9	183	85	91	1891
8 - 9.9	199	99	99	2093
10 - 11.9	210	103	103	2179
12 - 13.9	222	118	118	2422
14 - 16.9	223	130	129	2573

In the insulin program a relatively large variety was used. A considerable number of children were shifted to NPH insulin either alone or mixed with regular insulin. When the children were well regulated it was found that NPH insulin alone was prescribed for fifty-three, a mixture of NPH and crystalline for forty-six, and crystalline insulin plus protamine zinc insulin by separate injection for thirty others. Three were on globin insulin, two on mixtures of protamine zinc insulin and crystalline insulin, and one on protamine zinc insulin alone. These too were well regulated.

It was shown that in many children a single injection of NPH insulin daily would provide as good a control of the diabetes as the giving of crystalline and protamine zinc insulin by separate injections. This was found to be particularly true in those children for whom the ratio of crystalline to protamine zinc insulin had been 1:3 or less. In general when the proportion of crystalline to protamine zinc insulin had exceeded this, the addition of a small amount of crystalline insulin to the NPH type brought about the desired degree of control. Studies were carried out which indicated that such mixtures can be made with a preservation of most of the rapid action of the added crystalline insulin. In this type of control when combined with the dietary regulation listed above less than 2 gms. sugar appeared in the urine in one-third of the daily measurements. Considering the degree of severity and instability of diabetes in children, this degree of control is an excellent result. 2 gms. of glucose excreted in twenty-four hours represented about 1 % of the carbohydrate intake per day.

The number of authorities who favor insulin management alone with a free diet is steadily growing. The method is to allow the children to eat according to appetite with approximately the same limits of choice as non-diabetic children. The dose of insulin is adjusted to permit continuous mild hyperglycemia and glucosuria with precaution to avoid excessive glucosuria with attendant polyuria and especially to avoid acetoneuria. Frequent testing for acetone in the urine at home is carried on and this is the most important aid to the regulation of insulin dose. Analysis of diet records shows that the children spontaneously adjust to an intake of food that differs from the measured diets that were prescribed before the advent of the free diet method. It has been shown that infants and children on this regimen grow well with minimum ill-health. Hypoglycemic reactions of all degrees are rare and emotional disturbances attributed to mild hypoglycemia have been noticeably less among the

diabetic children on the free diet than those on whom a regulation of insulin plus diet is used. This was reported from a clinic in Cincinnati, Ohio, where both methods were compared.

In a study made by Meyer in Sweden, the following was reported: Fifty diabetic children were all treated without diet and with protamine insulin or protamine zinc insulin. It was found that fifteen children reached a constant level of insulin within two months after the beginning of treatment with insulin while thirty children had attained this level within six months; in only five children did the stabilization become evident after twelve months. The insulin levels below 30 units showed a tendency toward a shorter initial period than the levels above 30 units.

In a treatment reported by Guest of two infants the following was reported: Treatment was started immediately when glucosuria was discovered. Both were fed normal diets without restrictions. One was breast fed for ten months on demand schedule receiving one and two units of protamine zinc insulin daily. One at the age of three-and-one-half years and the other at the age of one-and-three-quarter years were both receiving 8 units of protamine zinc insulin and 6 units of regular insulin daily; a dosage that allowed for continued mild glucosuria. Neither child has ever suffered from acidosis despite several intercurrent infections. Growth has been normal.

In a report by A. Lichtenstein in 1949, the author supports the free diet theory. He points out that the amount of insulin required is about the same as children on a restricted diet. Much emphasis is given to the psychological considerations favoring a free diet. The psychological problems of the diabetic child are great and will be discussed later.

C. HYPOGLYCEMIA

That a "reaction" due to hypoglycemia will occur at some time to the diabetic child is almost unavoidable. No type of insulin has been shown to initiate milder or less numerous hypoglycemic shocks. A child can be trained to recognize the symptoms of weakness and faintness and by the eating or drinking of a few gms. of glucose in food or in liquid he can usually avoid the more serious loss of consciousness or convulsion which may require the administration of epinephrine or intravenous glucose.

COMPLICATIONS

If the prevention of hypoglycemia and acidosis on a day to day basis were the only problems in regard to the diabetic child, he would certainly have a bright future.

Unfortunately, there are secondary conditions which often are more disastrous than the diabetes itself. The prognosis of diabetes in childhood is, taking the long view, in spite of the progress of dietary and insulin treatment more adverse than had originally been expected. Late complications arising after fifteen to twenty years have often been described in the literature. Among the late complications is the well-known occurrence of tuberculosis and nephropathy. This may take the form in children of intercapillary glomerulosclerosis as described by Kimmelstiel and Wilson. Polyneuritis is also seen in young people with diabetes. Ocular complications are often found. A survey of complications in juvenile diabetes was made by Chute in Toronto in 1948.

He divided his subjects into two groups; one, those who had diabetes for more than fifteen but less than twenty years and another, those who had had diabetes for more than twenty years. His findings are summarized in the following tables:

I. Those with diabetes for less than twenty years in which group there were fourteen subjects (nine men and five women)

Complication	No. of Men	No. of Women	Total	Percent
Retinal hemorrhage	2	1	3	21
Retinal exudate	3	0	3	21
Opacity of the lens	0	2	2	14
Hypertension	1	0	1	7
Albuminuria	1	2	3	21
Arteriosclerosis	1	1	2	14
Absence of knee or ankle reflex	2	1	3	21
No demonstrable disease	5	2	7	50

II. Those with diabetes for more than twenty years in which group there were thirteen patients (seven men and six women)

Complication	No. of Men	No. of Women	Total	Percent
Retinal hemorrhage	4	1	5	38
Retinal exudate	4	1	5	38
Opacity of the lens	3	1	4	31
Enlargement of heart	2	0	2	15
Hypertension 160/100	3	1	4	31
Albuminuria	4	1	5	38
Arteriosclerosis	2	2	4	31
Bronchiectasis	0	1	1	8
Epilepsy	0	2	2	15
Absence of knee or ankle reflex	3	3	6	46
No demonstrable disease	1	1	2	15

That the incidence of complication increases with the duration of the disease is clearly shown by the two tables. The above observations are the more striking when one remembers that the oldest patient in this series was only forty and the youngest, twenty years of age. The average age was twenty-nine years.

The level of control as well as the duration of the disease is an important factor influencing degenerative changes and good control will delay and possibly prevent such changes. Present knowledge makes it not only possible but practicable to maintain a high level of control of diabetes in children. A high level of control appears to offer the best means of averting or delaying chronic degenerative changes.

In a study made on twenty-five patients, all of whom were juvenile diabetics who had had the disease from eleven to twenty-eight years, Grazel and Warschall reported that in none of the patients whose control was considered good did detectable vascular lesions develop. The report did not question that the incidence of diabetic complications increases with the duration of the disease but it pointed out that good control would probably postpone the onset of diabetic complications in a significant number of cases and in a similar manner lessen the severity of these complications.

In a study made by Daeschner, Deisher and Hartmann, the authors report on 120 children who had had diabetes. They ranged in age from eight to fifteen years. It was shown that the evidence of complication in diabetes is affected by the duration of the disease and the care exercised in its control. One of the problems pointed out in this report is the difficulty to exercise control over patients between the ages of fifteen and nineteen because of a rebellious and uncooperative attitude on the part of the adolescent.

Gangrene

Whitaker reported three cases of superficial gangrene in adolescent diabetes. The first patient was a boy of fifteen with diabetes of three years duration who was admitted to the hospital in coma. Despite good nursing attention a large area of gangrene involving the right buttock suddenly appeared and later became secondarily infected. The second patient was twenty-four years old and was also admitted in coma. An area of dry superficial gangrene developed on the anterior surface of the knee. Healing required six weeks. The third was a patient twenty-nine years old who by mistake injected insulin intra-dermally. There resulted small round patches of dry superficial gangrene at the sites of injection.

Skeletal Age

Hernberg and Heikel made a study of the skeletal age in diabetic children, thirty-five girls and forty-six boys, whose age ranged from nine months to fifteen years.

Some acceleration was observed in 16 %, retardation in 20 % and normal conditions in 65 %. In the majority of cases the retardation seemed to occur in connection with acidosis. In early childhood, these authors feel that the retardation was perhaps due to some endocrinal factor following hepatomegaly. The cause of acceleration is unknown and no definite relationship between the duration of the disease and abnormal skeletal variations was revealed.

Hypoglycemic Complications

The use of insulin which has saved so many lives since 1922, also has its drawbacks. Hypoglycemia, which is very difficult to avoid at some time in the management of the diabetic child, can cause great harm. In juvenile diabetes cerebral damage may result with relative ease because of hypoglycemia. Children seem to do better on insulin therapy providing a higher ration of crystalline to protamine zinc than is commonly used for adults.

PSYCHOLOGICAL PROBLEMS

It is generally recognized that psychological problems are commoner in diabetic than in non-diabetic children. This is not surprising when one considers the restrictions in relation to diet, the inconvenience and pain of insulin injections, the relative rigidity of the diabetic life with the necessity for urine and blood tests, and the natural dislike of the child to be different from others. Added to this, is the factor that often children are harmed because of overprotection on the part of their parents. These psychological traumas are accentuated if the child has experienced serious complications from time to time such as severe acidosis and frequent insulin reactions. Some children compensate by developing certain skills such as painting and music and others plunge into various hobbies. A large group, however, present special behaviour problems which take the form of antagonistic and resentful attitudes with resistance to authority and discipline. It is noteworthy that children whose behaviour problems are most acute are most difficult to handle during insulin reactions. It is evident that much could and should be done in the way of psychiatric assistance.

CASE HISTORIES

From the records of the "Jenner Kinderspital" in Berne, I have selected ten case histories of diabetic children. Some of the data in these case histories will now be presented. There are a number of conclusions which can be accurately drawn from

these case histories but there are some which if not qualified, are highly misleading. As an example the weight of the child may be cited. It has been previously stated that the diabetic child is heavier than the non-diabetic child. This is, of course, applicable only after regulation has taken place. The figures given in the case histories were taken shortly after the admission or upon the release of the child from the "Jenner Kinderspital". Inasmuch as loss of weight is a dominant symptom in the initial diabetic attack these weight figures do not necessarily conflict with those cited earlier in this paper. Complications which developed after years of diabetes or through poor regulation were, of course, limited.

CASE I

A girl who developed the condition at the age of eighteen months. Her weight was 11,5 kg. as compared with a norm of 10,2. Her height was 78 centimeters. The symptoms she showed at the time of the attack were slight fever, insomnia, irritability, acidosis, and glucosuria. There was no albumine in the urine, hemoglobin value was 79 % with a red cell blood count of 3,9 million. The child was stabilized on a diet of 920 Calories which were given as follows: carbohydrates 115 gms., protein 34 gms., fat 23 gms. The insulin employed was the regular type which was given in two doses, one of ten units in the morning and one of five units in the evening. After the onset of the diabetes strabismus was noticed which may point to a disturbance in the pituitary as the common cause of the diabetes and the ocular disturbance. There was no family history of diabetes.

CASE II

A girl who developed diabetes at the age of three years. Her weight was 14 kg. as compared with a norm of 13,2. Her height was 94 centimeters as compared with a norm of 91. The symptoms at onset were high fever, acetone vomiting, pharyngitis, glucosuria and acetone in the urine. There was no albumine. Hemoglobin value was 80 % with a red blood cell count of 3,9 million. The child was stabilized on a diet of 1400 Calories which were divided as follows: carbohydrate 140 gms., protein 42 gms., fat 35 gms. No insulin was needed to secure stabilization. There was no family history of diabetes.

CASE III

A girl who developed diabetes at the age of six. Her weight was 22 kg. as compared with a norm of 20. Her height was 135 centimeters which is the norm. The symptoms she developed were polydipsia, malaise, polyuria, glucosuria, acetonuria and polyphagia. There was no albumine in the urine. Hemoglobin value was 89 % with

a red blood cell count of 4,5 million. The child was regulated on a diet of 1675 Calories which were divided as follows: carbohydrate 220 gms., protein 66 gms., fat 44 gms. The type of insulin used was the regular insulin with two injections of ten units daily. Since then the child has died in diabetic coma. There was no family history of diabetes.

CASE IV

A boy who developed diabetes at the age of nine. His weight was 26 kg. which is normal for this age. The symptoms present were irritability, loss of weight, polydipsia, polyuria and nausea. Glucosuria and acetonuria were present. There was some albumine in the urine. Hemoglobin and red blood cell count were not measured. The child was regulated on a diet of 1895 Calories which was given as follows: carbohydrate 260 gms., protein 78 gms., fat 55 gms. Novo insulin was used. It was given in two doses, one of thirty units and one of twenty. There was no family history of diabetes.

CASE V

A boy who was stricken at the age of ten. His weight was 25,7 kgs. as compared with a norm of 31,2. His height was 134 centimeters as compared with a norm of 136. The symptoms at the time of the attack were high fever, grippe, polyphagia, polydipsia, polyuria, glucosuria and acetonuria. There was no albumine in the urine. Hemoglobin value was 88 % with a red blood cell count of 4,3 million. The child was regulated on a diet of 1430 Calories which was given as follows: carbohydrates 260 gms., protein 52 gms., fat 52 gms. The type of insulin used was the Novo variety which was given in a single dose of five units. There was no family history of diabetes.

CASE VI

An interesting case was that of an eleven year old girl who developed many of the symptoms of diabetes; malaise, unconsciousness, glucosuria and acetonuria. Her weight was 26,1 kgs. as compared with a norm of 32 kgs. Her height was 145 centimeters as compared with a norm of 137 centimeters. There was no albumine in the urine. Hemoglobin was 91 % with a red blood cell count of 4,6 million. In the hospital the acetone and sugar quickly disappeared but a high percentage of phosphorous was discovered in the urine. The diagnosis was not one of Diabetes Mellitus but one of alimentary glucosuria which is frequent in the leptosome type due to disturbance in vegetative function. The child has since recovered. Therapy consisted of a diet rich in protein plus the administration of citropepsin.

CASE VII

A girl who developed diabetes at the age of 11. Her weight was 30 kgs. as compared with a norm of 29. Her height was 142,5 centimeters as compared with a norm of 132. She showed the following symptoms in the initial attack: polydipsia, dysphagia, malaise and a slight cold. A hyperkeratosis due to a vitamin A deficiency and fissures about the mouth due to a vitamin B2 deficiency were corrected in the hospital. The child showed both glucosuria and acetonuria but no albuminuria. Hemoglobin value was 86 % with a red blood cell count of 4,4 million. The child was stabilized on a diet of 1890 Calories consisting of 300 gms. carbohydrates, 60 gms. protein, 45 gms. fat. Insulin used was the Novo type with a single dose of 16 units per day. There was no family history of diabetes.

CASE VIII

A girl who developed the condition at the age of eleven. Her weight at the age of 12 1/2 was 32,5 kgs. as compared with a norm of 37. The symptoms at the time of the original attack were loss of weight, polydipsia, with both glucosuria and acetonuria. Albumine was found in the urine. Hemoglobin value was 90 % with a red blood cell count of 4,5 million. The child was regulated on a diet of 1845 Calories which consisted of 280 gms. carbohydrates, 75,5 gms. protein, 38,5 gms. fat. Insulin used were of the Novo and protamine type with two injections of twenty units each. Frequent infection, especially paronychia, have since been noticed. The only family record of diabetes was that of a maternal aunt who developed the condition at the age of 60.

CASE IX

A girl who developed diabetes at the age of fourteen. Her weight was 48 kgs. as compared with a norm of 47. Her height was 168 centimeters as compared with a norm of 155. The symptoms at the time of the initial attack were irritability, polydipsia, polyphagia, nausea, loss of weight, glucosuria and acetonuria. There was no albumine in the urine. Hemoglobin value was 92 % with a red blood cell count of 4,8 million. The girl was regulated on a diet of 2100 Calories which were given as follows: 320 gms. carbohydrate, 70 gms. protein, 60 gms. fat. Twenty units of globin insulin were given per day. After the onset of diabetes a tendency towards frequent infection was noticed. There was no family history of diabetes.

CASE X

A boy who developed diabetes at the age of ten. His weight at 11 1/2 years of age was 33,1 kgs. as compared with a norm of 34 kgs. His height was 145 centimeters

as compared with a norm of 140 centimeters. The symptoms at the time of the first attack were polydipsia, polyuria, polyphagia, and loss of weight. Glucosuria and acetonuria were present. There was some albumine in the urine. Hemoglobin was 92 % and the red blood cell count was 4,8 million. The boy was regulated on a diet of 2000 Calories that were given as follows: 330 gms. carbohydrates, 65 gms. protein, 35 gms. fat. Forty-eight units of globin insulin were injected daily. As a sequel to the diabetes pruritus and frequent infection have occurred. There was no family history of diabetes.

In summarizing these case histories:

1. Nine cases of true diabetes
2. Six girls and three boys
3. Age at onset from 1 1/2 - 14 years
4. Height and weight above normal
5. Slightly low hemoglobin and red blood cell values
6. Symptoms:

a) loss of weight	4
b) polydipsia	7
c) polyphagia	4
d) polyuria	4
e) irritability	3
f) acidosis	8
g) fever	3
h) insomnia	1
i) cutaneous involvement	3
j) albuminuria	3
k) respiratory infection	3
l) malaise	4
m) dysphagia	1

7. Only one case where there is any family history
8. Treatment at the "Jenner Kinderspital" consists of a combination of diet and insulin regulation. Enough food is given to insure adequate growth and the insulin dosage necessary to maintain a mild glucosuria is given.

That only one of these children had any history of diabetes in the family was the unusual element in these case studies. In comparison with a figure of 62 % found in the United States this figure is extremely small. While not disproving the importance of heredity in the diabetic child, it is quite clear that this is far from the only entity which determines which child shall remain free and which child shall develop Diabetes Mellitus.

SUMMARY

In looking back we can see how the lot of the diabetic child has changed since the discovery of insulin. Many aspects of the disease are still under discussion. The importance of various etiological factors, heredity, infection, and nervous system disorders have been discussed. In studies in the United States, heredity seems to be a dominant factor. In the 10 cases used in this paper plus 6 additional ones studied at the "Jenner Kinderspital" the importance of heredity was not demonstrated. Because of the relatively small number of cases evaluation is difficult. The acute symptoms of childhood diabetes have been discussed. Physical and laboratory findings have been discussed. The complexity of treating the child was brought out by showing the disagreements in the free as opposed to regulated diets. Long range complications in spite of successful management have been presented. Psychological problems of the diabetic child have also been discussed. The data used was from studies all over the world with case histories taken from the "Jenner Kinderspital" in Berne.

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